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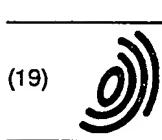
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(19)

European Patent Office

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(11)

EP 0 429 842 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention  
of the grant of the patent:  
28.08.1996 Bulletin 1996/35

(51) Int. Cl.<sup>6</sup>: A61N 1/30

(21) Application number: 90120162.4

(22) Date of filing: 20.10.1990

(54) Device for the transdermal administration of protein or peptide drug

Vorrichtung zur transdermalen Applikation von Protein- oder Peptid-Medikamenten

Dispositif d'administration transcutanée de médicaments à base de protéine ou de peptide

(84) Designated Contracting States:  
BE GB IT

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(30) Priority: 27.10.1989 KR 8915519  
22.05.1990 KR 907357

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(43) Date of publication of application:  
05.06.1991 Bulletin 1991/23

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EP-A- 0 308 572	DE-A- 2 643 130
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EP 0 429 842 B1

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**Description**

The invention relates to the transdermal administration device for administration of a protein or peptide drug and more particularly, to a device for transdermally administering the ionized drug by electric force after dissolving and ionizing a protein or peptide drug with an ionizing solvent.

Generally, in delivering of a protein or peptide drug (i. e. insulin as physiological metabolism modulator, interferon as anticancer agent, and captopril as cardiovascular modulator) into the human body, some administration methods such as oral administration, injectables, mucosa delivery agent and pump transplant have been commonly used, but such methods caused some side effects and their use was inconvenient, let alone the psychological discomfort to patients.

To comply with this matter, some researchers have recently studied the transdermal administration method of delivering a protein or peptide drug into skin. Among other things, a most attractive method is transferring a protein or peptide drug having electric charge into the epidermis by an electric current.

For instance, R. L. Stephen et al, Biomed. Biochem. Acta 43 (1984) 5, 553 - 558, tried to deliver insulin into a pig's skin through the transmission of constant electric current but the result was unsucces due to the insufficient electric charges of insulins and to the failure of making its monomer.

Thereafter, another method to deliver the insulins into the human body by removing the stratum corneum was made but this method has been associated with some problems including infections incurred out of removing epidermis and the undesirable transformation/treatment of the skin. Also, the method of delivering insulin without any skin bruise was studied again by using pulse current. However, this proved to be inefficient because of the insufficient dose of the drug delivered and short duration of drug effect in the body.

In the meanwhile, R. R. Burnette and D. Marerro, J. Pharm. Sci., 75: 738 (1986) experimented to transdermally administer TRH (Thyrotropin releasing hormone), a hormone of extending by iontophoresis the pregnancy and lactation of women. Further, J. E. Marchand and N. Hagino, J. Urol. 97: 874 (1982) exemplified in animal experiment the possibility of administering Vasopressins into the skin.

Also, B. Robert Meyer et al, clin. pharm & Therape, 44, 6, 607 (1988) tried to deliver LH (Luteinizing Hormone) across the skin by a direct current.

However, the aforementioned methods have recognized several disadvantages as follows: When a protein or peptide drug is delivered transdermally, its molecular chains are susceptible to being destroyed by electric current and the depression of biological activities occurred. Moreover, since the delivery of required amount is not available once a time because of the high permeation resistance in skin, only a small percentage of the drugs should be transdermally delivered in several divided times. Besides, the transdermal delivery might raise other specific problems such as skin irritation/impairment and more potent use of enhancer might also induce the deformation of human skin system.

The EP-A-0 308 572 discloses an iontophoresis device comprising an electrical power source, a pulse generator for producing therapeutic pulses, a working electrode and a counter electrode, the pulse generator producing reverse pulses in an intermission period between the therapeutic pulses to remove residual charge between the electrodes. This device comprises a transdermal administration device as patch-type having an electrode being open to the outside and a drug reservoir.

One of the objects of the present invention is to provide an efficient method, wherein by skin stimulating needle (hereinafter "skin needle"), a sufficient amount of protein or peptide drug can be transdermally delivered into the skin on a continual basis with reduced side effects.

It is another object of the present invention to provide a transdermal administration device comprising the storage reservoir of ionizing solvent, drug reservoir and skin needle, through which the sustained administration of a protein or peptide drug may be available for three to four days by a simple one-time treatment.

The detailed description of this invention is as set forth hereunder:

The invention relates to the transdermal administration of a protein or peptide drug by the following procedure: Contacting and ionizing a protein or peptide drug immersed in polyelectrolyte with the composition of ionizing solvent consisting of solvent, polyelectrolyte and enhancer, and forming the drug delivery pathway into the skin by an electric razor, and penetrating the above ionized drug into the skin by electric force.

One embodiment of the transdermal administration device according to this invention is an integration-type transdermal administration device as patch-type used by attaching to the skin, comprising an electrode being open to the outside and a drug reservoir which comprises

A) a solvent reservoir (2) of ionizing solvent on the upper side forming electrode (1),

B) a drug-immersed hydrophilic polymer drug reservoir (3) forming the lower part of the solvent reservoir,

C) a water-swelling polymer skin needle supporter (5) where a plurality of skin needles (4) are vertically dispersed in a fixed state,

- D) a stacking-structure adhesive layer (6) formed around the said skin needle supporter (3), and
- E) solvent inlet (7) placed in the upper central part of the said solvent reservoir (2).
- 5 Another embodiment of the transdermal administration device according to this invention is a separation-type transdermal administration device as patch-type used by attaching to the skin, comprising an electrode being open to the outside and a drug reservoir in which:
- A) a solvent reservoir (12) of ionizing solvent on the upper side forming the electrode (11),
- 10 B) a semipermeable membrane (18) with a molecular cut-off ranging from 200 to 20.000 while forming the lower side of the solvent reservoir (12),
- C) a drug-immersed hydrophilic polymer drug reservoir (13),
- 15 D) a patch body (30) composed of adhesive layer formed around the said drug reservoir (13), and
- E) aside from the patch body (30), a needle plate (15) in which a plurality of skin needles (14) on water-swelling polymer sheet are vertically distributed in a fixed state.
- 20 Within the device according to the invention there may be used a ionizing solvent, in line with the solvent dissolving and ionizing a protein or peptide drugs, which consists of: in proportion to water 100 % by volume, 1 to 50 % by volume of any one or more mixture solutions selected from sodium acetate, sodium-EDTA, sodium salicylate, salt buffer solution of phenol derivatives, acetic acid, hydrochloric acid, ammonia water, and caustic soda; 1 to 30 % by volume of polyelectrolyte: 1 to 30 % by volume of enhancer. The function of said ionizing solvent is: Dissolving a protein or peptide drug having more than three peptide units of amino acid into the monomer, and increasing a ionization degree, and enabling the said drug to efficiently pass through the epidermis layer.
- The use of the devices according to the invention to the transdermal administration method of a protein or peptide drug can be shown by the following procedure: Contacting and ionizing a protein or peptide drug immersed in polyelectrolyte with the composition of ionizing solvent consisting of solvent, polyelectrolyte and enhancer, and forming the drug delivery pathway into the skin by an electric razor, and penetrating the above ionized drug into the skin by electric force.
- This invention can be described in more detail as set forth hereunder:
- In general, a protein or peptide drug being used in the treatment of various human diseases has its innate isoelectric point wherein its dissolution is made available only in case of exceeding the isoelectric point or in a lower pH. Since such drug has a constant dipole polarity, the ionization of monomeric drug having the positive or negative electric charge depends on the pH of solvent.
- Therefore, in case a target drug having cation (less than the isoelectric point of the drug), anode is used and cathode used in anionic drug (more than the isoelectric point). Thus, a drug may be transferrable by an electric repulsion force.
- By applying such principle, a method of administering a protein or peptide drug across human skin is given: the ionizing solvent used in dissolving a protein or peptide drug into monomer having either cation or anion, uses the composition of ionizing solvent comprising the following: In proportion to water 100 % by volume, 1 to 50 % by volume of solvent, 1 to 30 % by volume of polyelectrolyte, and 1 to 30 % by volume of enhancer.
- 45 Here, the solvent of main ingredient may be used by selecting some organic/inorganic acids and organic/inorganic bases such as sodium acetate, sodium-EDTA, sodium salicylate, and salt buffer solution of phenol derivatives, acetic acid, hydrochloric acid, ammonia water, and caustic soda. However, in case of using cathode, the solvent such as inorganic or organic base or salt buffer solution should be used and in case of using anode, the solvent such as inorganic or organic acid be used.
- 50 In the electrode of polyelectrolyte which plays a role to prevent the pH change of solvent by electrolysis is anode, any one or more soluble (or insoluble) polymers may be used in the following: polyacrylamide (more than M. W. 10.000), polyvinylamine (more than M. W. 10.000), quadrivalent ammonium, or pyridinium. If the electrode is cathode, any one or more solvents may be used as the pH-controlling polyelectrolyte in the following: polyacrylic acid, carboxymethylcellulose (C. M. C.), alginic acid. When the above polyelectrolyte is added, the pH change of electrode is described in Table I.

Table 1

pH Resistance of 1 % polyelectrolyte solution after applying 1 mA current for 2 h		
Polyelectrolyte	pH Change of Cathode	pH Change of Anode
Polyacrylamide	-	7.5 → 9.1
Polyvinylamine	-	7.5 → 7.9
Polyacrylic acid	7.0 → 6.6	-
C. M. C.	7.0 → 4.3	-
Alginic acid	7.0 → 4.4	-
D. I. Water	7.0 → 1.8	7.5 → 12.5 /5

In order to facilitate the drug delivery, any one or more enhancers is/are used by selecting the following:

- 20 a) EDTA as chelating agent, citric acid, N-alkyl derivative
- b) bile salts (sodium dioxychelate, sodium tarocholate)
- c) fatty acids (oleic acid mono-olein, saponin)

Meantime, in this invention, the electric current having a density ranging from 0.01 to 1 mA/cm should be used. And  
 25 a pulsating current in its type is more preferable than a direct current because the occurrence of impedance by the current leads to the great increase of resistance and voltage, thus being vulnerable to skin burn, while the pulsate current source to eliminate the impedance wherein high currents may be available under the low voltage.

By way of example to make the operation of the invention more clear, reference is made to the accompanying drawings.

#### 30 Brief Description of the Drawings

- Fig. 1 is a vertical section of an integration-type transdermal administration device as one embodiment according to this invention.
- 35 Fig. 2 is a vertical section of a separation-type transdermal administration device as another embodiment according to this invention.
- Fig. 3 is a graph showing the change of blood glucose level with the lapse of time when insulin is administered  
 40 transdermally in accordance with Example 4 of this invention.

- 1, 11      Electrode
- 2, 12,     Solvent reservoir
- 3, 13, 23   Drug reservoir
- 45 4, 14     Skin stimulate needle
- 5            Skin stimulate needle supporter
- 15           Skin stimulate
- 6, 16       Adhesive layer
- 7            Solvent inlet
- 50 9, 19       Released paper
- 18, 28      Semipermeable membrane
- 30           Patch body

Fig. 1 is an integration-type transdermal administration device embodying the concept of the present invention in which: Solvent reservoir (2) made of plastic film (e. g. polyethylene or polyethylene terephthalate), supporting the frame of device itself and having no solvent permeability and on the upper side, electrode (1) and solvent inlet (7) are open to the outside. The said electrode (1) consists of metal sheet comprising silver, lead or tin and the solvent inlet is made of "V" type rubber, so that under the air-tight condition from the outside, the composition of ionizing solvent may be injected into solvent storage reservoir (2) by a syringe.

In the lower part of the said solvent reservoir (2), drug reservoir (3) comprising drug-immersed (in powder) hydrophilic polymer layer is formed. The soluble polymers usable as the said drug reservoir (3) are polyacrylamide, carboxymethylcellulose, polyvinylimine, polyacrylate, alginate, karaya gum, and gelatin. The major functions of the water soluble polymer are to support the drug, heighten the drug permeability by hydrating the human skin.

5 In the skin needle supporter (5) stacked at the lower part of the said drug supporter (3), 1 to 15 pieces of skin needles (4) per the unit area (cm) is/are dispesed in a fixed state, of which length protruding to the outside of drug supporter should be 0.2 to 2 mm. The skin needle (4) according to this invention has the diameter ranging from 50 to 400  $\mu\text{m}$ , of which quality may be a sterilized stainless steel.

If the diameter of skin needle (4) exceeds 400  $\mu\text{m}$ , it is very difficult to permeate the skin and if smaller, the manufacture of skin needle is not easy. However, it appears that the thickness of skin needle (4) does not greatly affect the permeable amount of drug. Also, the protruding skin needle (4) in more than 2 mm long leads to the bruise of the capillary vessel in corium layer, thus causing a coagulation. If the length of skin needle is less than 0.2 mm, the needle cannot permeate the skin, thus resulting in a drastic decrease in delivering the amount of drug.

10 Should the distribution of skin needle (4) per unit area of skin needle supporter (5) be overly high, an excess of drug might be delivered and the skin's infection might not be neglected after treatment. However, if small, the drug delivery effect of substantial amount cannot be expected. The skin needle supporter (5) is made of water-swelling polymers and some of available polymer is the same as the case of drug reservoir (3).

15 The said skin needle supporter (5) is surrounded by the adhesive layer (6) which allows the attachment of an administration device to skin, and these skin needle supporter (5) and adhesive layer (6) are covered with released paper (9).

20 The use of an integration-type transdermal administration device is as follows: Injecting the ionizing solvent into solvent reservoir (2) through solvent inlet (7) by a syringe and so on, and removing released paper from the device, and compressing the device to the skin using adhesive layer (6). Then, connecting any one of anode or cathode to the electrode protruding on the upper side according to the kinds of drug or solvent, and having the opposite electrode connected to a conductive pad, e. g. karaya gum, etc. (not illustrated), then, attached to the side of the device, or connected to other device, then, usual two devices simultaneously.

25 In this way, the composition of ionizing solvent stored in solvent reservoir (2) dissolves the drug containing in drug reservoir (3), and ionizes the drug into cation or anion; the ionized drug moves to the skin by the electric force with the electrode (1).

30 Meantime, the skin needle (4) attached to skin needle supporter (5) may penetrate the epidermis layer by compression power, when the administration device is attached to the skin, thus forming the pathway for the drug delivery. With the lapse of time, when a solvent permeates from solvent reservoir (2), the skin needle supporter (5) becomes swelled by water swelling effect and the skin needle comes out from the skin.

35 However, if no electric current is applied to the pathway formed by skin needle (4), drugs claimed in this invention cannot penetrate across the skin mainly because the hydrophobic epidermis layer does not allow the permeation of hydrophilic drug and the path way formed by skin needle (4) is temporary closed by the swelling of skin.

40 Therefore, the electric current applied in the device makes the ionized drug and solvent more toward the opposite electrode, and then, the hydrophilic protein and polypeptide of the skin become arranged in equilibrium toward cathode, which cause a "contraction" of the skin. By the above phenomenon, the pathway of epidermis layer becomes open and the drug in the pathway may penetrate into corium layer.

Meantime, Fig. 2 as enclosed herein is a separation-type transdermal administration device embodying another concept of the present invention in which a patch body and skin needle plate (15) are separated.

The said patch body is made of the following:

- 45 A) solvent reservoir (12) where ionization solvent is stored,  
 B) semipermeable membrane (18) consisting of the lower part,  
 C) drug reservoir (13) where the drug is dispersed,  
 D) adhesive layer (16),  
 E) released paper (19);

50 in addition to that, there several skin needles (14) are fixed vertically in the skin needle plate separated from the body frame.

The characteristics of a separation-type device are that since the ionizing solvent is already contained in the device, the administration of another ionizing solvent is unnecessary; there is a semipermeable membrane (18) between ionization solvent reservoir (12) and drug reservoir (13); there is a skin needle plate separated from the patch body.

55 The semipermeable membrane (18) whose molecular cut-off is in the level ranging from 200 to 20,000 is rather preferable, because the selection of semipermeable membrane (18) having less molecular cut-off than that of delivery drug prevents the reduction of drug activity as the drug is not mixed in solvent reservoir (12).

The semipermeable membrane to be used in this invention is selected from the following: polypropylene, cellulose, and ethylene vinylacetate. By making the molecular cut-off of semipermeable membrane smaller than that of drug and polyelectrolyte contained in ionizing solvent, the latter cannot permeate the membrane. Then, the pH of ionizing solvent remains unchanged and the skin irritation can be eliminated by preventing the contacts between polyelectrolyte and skin. Thus, the solvent molecule and enhancer only can pass through the semipermeable membrane (18).

5 The formation of skin needle plate (15) should be the same as that of skin needle placed in an integration-type administration device and the common type of textile fiber is rather advisable.

10 The method of using a separation-type administration device is as follows: Lightly compressing a skin needle plate (15) on the skin, and forming the drug delivery pathway on skin, and removing the skin needle plate (15), and on that skin, compressing the patch body (30) removing a release paper (19). The operation and principle of other parts are the same as those of an integration-type device.

15 The method of using a separation-type administration device is as follows: Lightly shaving the skin by a common type of razor without using the skin needle plate (15), and alleviating the permeation resistance of epidermis layer, and on that skin, compressing the patch body (30) removing a released paper (19).

Meantime, a protein or peptide drug applicable to this invention includes the following: as the drugs having more than three peptide bond units in amino acid, for example, cardiovascular modulator (captopril, bradykinin, atriopeptin, calcitonin gene factor, C. N. S. cholecystokinin (CCK-8, 32) as C. N. S. active peptide,  $\beta$ -endorphin, nerve growth factor, melanocyte inhibitor-I, gastric modulator (gastrin antagonists, neuro-tension, somatostatin), antibiotics & anticancer drugs (interferon, cyclosporin, encephalins), and biological metabolism modulator (albumin, insulin, vasopressins, oxytocin, growth hormone, LH (Luteinizing Hormone), TRH (Thyrotropin Releasing Hormone)).

20 Referring to the influx mass of a protein or peptide drug in this invention, the iontophoresis of the ionized drug can be described as follows:

$$25 J = -D \frac{de}{dx} + \frac{D_2 \cdot Z \cdot e \cdot E \cdot C}{KT}$$

Where M is the mass of the drug delivered. D is the diffusion coefficient of nonionized class, D is the diffusion coefficient of ionized class, Z is the number of electric charge in molecular, e is an ionized degree, E is a potential difference, C is the concentration of ionized class, K is a Planck's constant, T is an absolute temperature.

30 As shown in the above formula, a higher electric conductivity of solution makes the ionized classes dominate the diffusion in a more competitive manner. As a result, the diffusion of nonionized class can be neglected because of "dc/dx = 0". Thus, the above formula is expressed as follows:

$$35 J = \frac{D_2 \cdot Z \cdot e \cdot E \cdot C}{KT}$$

In general, there is a method of increasing the number of electric charge (Z) to heighten the electric current of ionized drug: in case the drug having limited number of electric charge is bound with the function group such as sulfate base having plentiful numbers of electric charge, the drug derivatives of increased numbers of electric charge may be obtained. Such drug derivatives may be more ionized than the general drugs which has relatively less number of electric charge among solvents and further, their competitive movement by being highly sensitive to the electric current results in increasing the mass of the drug delivered.

40 45 With reference to the ionized degree "e" as described in the foregoing, of its ionization rate will increase in accordance with the selection of ionizing solvent. Therefore, as the ionization solvent, organic/inorganic acid and organic/inorganic salt base may be used: at the case may be, it may be used as the type of salt such as sodium chloride, phosphate or organic acid salts.

The invention will now be illustrated by the following examples.

#### 50 Example 1

##### Manufacture of Integration-Type Administration Device

55 Adding an aqueous solution of 0.5 M sodium salicylate containing 1 % polyacrylic acid salts (brandname: Carbopol) into 100 IU/ml insulin, and dispersing this mixture evenly. Then, adding 3 mg/ml phenol and 16 mg/ml glycerin into this mixture and mixing them sufficiently at less than 10 °C, and thus, manufacturing the gel mixture of drug supporter.

On a sheet woven by polypropylene fibre, meantime, fixing 100  $\mu$ m of T-type skin needle in diameter in a range of 10 pieces/cm toward the bottom from the upside, and paving the opposite sheet phase of protruding skin needle with

the gel mixture of said drug reservoir evenly, and drying it by a freezing dryer, and thus, manufacturing both drug reservoir and skin needle supporter.

5 In a following manner, heat-sealing the said drug supporter and skin needle supporter to the lower side of already manufactured solvent storage reservoir by polyethylene terephthalate, and applying an adhesive layer and released paper to the fringe, and thus, manufacturing an integration-type administration device.

Meantime, the composition of ionizing solvent usable in the said integration-type administration device should contain 0.5 M sodium salicylate salt buffer solution containing 3 % polyacrylamid, 3 mg/ml phenol, 16 mg/ml glycerin, and 1 % saponin. Such ionizing solvent is added into the solvent storage tank prior to using the said integration-type device.

10 **Example 2**

**Manufacture of Separation-Type Administration Device (1)**

15 Adding the composition of ionizing solvent into polyethylene solvent reservoir attached with silver electrode, and heat-sealing in a row the cellulose membrane having a molecular cut-off of 3500 and already manufactured drug reservoir placed in the lower side. The composition of ionizing should contain citric acid at pH 3, 0.2 % polyacrylic acid (M. W. 150,000), 3.5 mg/ml phenol, 16 mg/ml glycerin, and a small amount of polyoxyethylene ether. The manufacture of drug supporter is as follows: Completely dissolving 100 IU/ml insulin and citric acid at pH 3 to porous polyurethane foam, mixing it with 10 % polyacrylate salts (brandname: Carbopol), and drying in a vacuum.

20 On a flexible aluminum foil, meantime, fix vertically T-shape skin needle in a range of 10 pieces/cm, and on the top of that, paving a sheet woven by polyester, and by completely fixing the said needle with adhesives, and thus, manufacturing the skin needle plate. The manufacture of other parts is the same as that of Example 1.

25 **Example 3**

**Manufacture of separation-Type Administration Device**

The composition of ionizing solvent compositions should contain 1 M sodium acetate, 0.1 % polyethyleneimine (M. W. 200,000), 3 mg/ml phenol, 16 mg/ml glycerin, and a small amount of monoolein.

30 Semipermeable membrane should use the cellulose membrane having the molecular cut-off of 1,000. The manufacture of drug supporter is as follows: Adding 35 % alginate gel containing 1 M sodium acetate into 100 IU/ml and a small amount of phenol & glycerin, and mixing this mixture sufficiently, and drying it by freezing.

35 **Example 4**

**Use of Integration-Type Administration Device**

40 Shaving around the back hair of a white New Zealand-origin rabbit, and measuring its blood glucose, and attaching it to an integration-type administration device as manufactured in accordance with Example 1. Then, attaching cathode to the electrode, and having anode of the opposite connected to E.C.G electrode (brandname: Biolect) made from karaya gum, and transmitting the electricity of 0.5 mA, 2 KHz for 20 min.

As a result of conducting the said procedure concerning 20 experiment animals, it was noted that the average blood glucose level was decreased from 100 mg/dl to 60 mg/dl within 6 h. And such effect was maintained for 12 h. The Fig. 3 table as enclosed herein illustrated the result of this example.

45 **Example 5**

**Use of separation-Type Administration Device**

50 Shaving around the back hair of a white New Zealand-origin rabbit, and lightly compressing a skin needle plate of a separation-type administration device as manufactured in accordance with the said Example 2, and removing the plate, and on the top of that, attaching a patch body.

Then, attaching cathode to the electrode, and having anode of the opposite connected to E. C. G. electrode, and transmitting the electricity of 0.5 mA, 2 KHz for 20 min.

55 As a result of measuring the average blood glucose level concerning 20 experiment animals, it was decreased from 100 mg/dl to 50 mg/dl within 4 h. And such effect was maintained for 12 h.

**Example 6****Simultaneous Use of Both Integration- and Separation-Type Administration Devices**

5 By attaching cathode to an integration-type administration device of Example 1 and having anode of the opposite connected to a separation-type administration device, the experiment was conducted in a same way as did in both Examples 4 and 5.

As a result of measuring the average blood glucose level concerning 20 experiment animals, the said level was decreased from 100 mg/dl to 30 mg/dl within 4 h. 17 animals among them were dead due to hypoglycemia within 8 h.

**Example 7****Use of Electric Razor**

15 This example was conducted in a same way as did in Example 5 using a separation-type administration device in Example 2: Shaving the back hair of a rabbit by an electric razor instead of the skin needle plate, and attaching it to a patch body of a separation-type administration device.

As a result of measuring the average blood glucose level concerning 20 experiment animals, it was decreased from 100 mg/dl to 50 mg/dl within 4 h. 15 animals among them showed less than 20 mg/dl hypoglycemia within 2 h.

**Examples 8 to 11**

25 This example was conducted in vitro with a separation-type administration device in Example 2 by changing any administered drugs into insulin (Example 8), T. R. H. (Example 9), L. H. (Example 10), and calcitonin (Example 11, respectively).

Fixing the outer surface of mouse skin to the adhesive part of administration device, and fixing the diffusion cell adding saline solution in the inside, and treating it by the electric current of 0.1 mA for 20 min while connecting an administration device and diffusion gel to the electrode.

30 The drug in a diffusion cell delivered through the mouse skin was separated and assayed by HPLC and the result was described in Table 2.

Tabelle 2

Drug Delivery in Diffusion Cell Through the Mouse Skin				
Hour	Exam. 8 (Insulin/IU)	Exam. 9 (TRH/mM)	Exam. 10 (LH/mM)	Exam. 11 (Calci- tonin/IU)
2	3.0	22	8	4
4	4.4	31	12	10.5
8	9.8	45	15	15.1
12	12.4	70	16	26.7
18	14.7	83	21	32.1

A transdermal administration method for protein or peptide drug according to this invention has the following merits:

a) may prevent the transformation of drug, by separating the ionizing solvent from the drug and avoiding a contact between the drug and electrode,

b) may prevent the reduction of drug's activity owing to the pH change of solvent by using a pH-controlling polyelectrolyte.

55 Further, since a drug is immersed in a water-soluble polymer, the skin-administration effect of drug can be enhanced by contacting a high-concentrated drug with the skin and hydrophilizing the skin. Furthermore, the use of a skin needle and/or razor makes it possible to form the drug delivery pathway on epidermis, thereby solving the following specific problems as shown in the transdermal administration of protein or peptide drug, i. e. insufficiently of drug delivered, the transformation of skin by owing to chemical enhancer or electric irritation, and the reduction of drug's activity

in the skin. Along these lines, the sustained transdermal administration of the said drug may be available for three or four days by one-time use.

Meantime, the comparison between the skin treatment of razor and drug administration of skin needle according to this invention is shown below.

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Data on the delivery effect of insulin based upon the skin treatment by using a skin needle and razor			
Hour	Control (No Insulin)	Blood Glucose Level of Rabbit (mg/dl)	
		Skin Needle	Razor
0	115	104	104
2	115	54	64
4	110	66	53
6	99	52	47
8	103	60	40
10	102	65	11

Remarks:

- a) Condition of electric current: 0.5 mA, on/off = 1
- b) Treatment time: 20 min
- c) Skin needle: 3 pieces/cm
- d) Razor: Treated by an electric razor for 20 sec

Hour	Blood Glucose Level of Rabbit (mg/dl)				
	2 sec	10 sec	20 sec	40 sec	60 sec
0	107	125	104	119	101
2	88	105	64	70	86
4	100	91	53	55	71
6	92	86	47	17	41
8	87	88	40	low	24
10	113	72	11	dead	dead

The delivery effect by the razor has not been fully established in its mechanism. We assume that like that of skin needle, the mechanism by the razor might be as follows: Reducing the resistance of drug's permeability into the skin, facilitating the electric current and thus, easily permeating the drug into the skin.

The thickness of epidermis is, even if variable, said to be in the range of 0.2 to 0.01 mm. By treating the epidermis by a razor, the upper part is partially removed and results in increasing the permeability of drug and electric conductance. In other words, similar case can be seen that an alcoholic lotion treatment after shaving gives a feeble irritation.

In case of a skin needle, although there is little skin resistance in the permeation pathway across the skin, the whole delivery effect is negligible small because of a limitation of usable skin needles. The blood glucose level of rabbit treated by an electric razor is lower than that of skin needle, which may be due to the fact that electric razor gives large surface area of treated skin compared to that of skin needles.

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#### Claims

- An integration-type transdermal administration device as patch-type used by attaching to the skin, comprising an electrode (1) being open to the outside and a drug reservoir (3) characterized by

A) a solvent reservoir (2) of ionizing solvent on the upper side of which solvent reservoir the electrode (1) is formed,

B) a drug-immersed hydrophilic polymer drug reservoir (3) forming the lower part of the solvent reservoir (2),

C) a water-swellable polymer skin needle supporter (5) comprising a plurality of skin needles (4) vertically dispersed in a fixed state,

D) a stacking-structural adhesive layer (6) formed around the said skin needle supporter (5), and

E) a solvent inlet (7) placed in the upper central part of the solvent reservoir (2).

2. A device as claimed in claim 1, in which the drug reservoir (3) and the skin needle supporter (5) are composed by any one or more polymers: polyacrylamide, carboxymethylcellulose, polyvinylimine, polyacrylate, alginate, karaya gum, and gelatin.

3. A device as claimed in claim 1, in which the skin needle supporter (5), 1 to 15 pieces of skin needle (4) per the unit area (cm) is/are attached, and the skin needle (4) has the diameter ranging from 50 to 400 µm and its length protruding to the outside of drug supporter is 0.2 to 2 mm.

4. A separation-type transdermal administration device as patch-type used by attaching to the skin, comprising an electrode (11) being open to the outside and a drug reservoir (13) characterized by

A) a solvent reservoir (12) of ionizing solvent on the upper side of which solvent reservoir the electrode (11) is formed,

B) a semipermeable membrane (18) with a molecular cut-off ranging from 200 to 20,000 while forming the lower side of the said solvent reservoir (12),

C) a drug-immersed hydrophilic polymer drug reservoir (13),

D) a patch body (30) composed of adhesive layer formed around the said drug reservoir (13), and

E) aside from the patch body (30), a needle plate (15) in which a plurality of skin needles (14) are vertically distributed in a fixed state.

5. A device as claimed in claim 4, in which the semipermeable membrane (18) is in the group of polypropylene, cellulose, and ethylene vinylacetate.

#### 40 Patentansprüche

1. Vorrichtung zur transdermalen Verabreichung vom Integrationstyp, die als Lappentyp durch Befestigung auf der Haut verwendet wird, mit einer nach der Außenseite hin offenen Elektrode (1) und einem Arzneimittelvorratsbehälter (3), gekennzeichnet durch

A) einen Lösungsmittelvorratsbehälter (2) für ionisierendes Lösungsmittel, auf dessen Oberseite die Elektrode (1) ausgebildet ist,

B) einen von Arzneimittel überfluteten Arzneimittelvorratsbehälter (3) aus hydrophilem Polymer, der den unteren Teil des Lösungsmittelvorratsbehälters (2) bildet,

C) einen Hautnadelträger (5) aus in Wasser quellbarem Polymer, der mehrere Hautnadeln (4) umfaßt, welche in einem fixierten Zustand vertikal verteilt sind,

D) eine Klebstoffschicht (6) mit geschichteter Struktur, die um den Hautnadelträger (5) herum ausgebildet ist, und

E) einen Lösungsmittelleinlaß (7), der in dem oberen mittigen Teil des Lösungsmittelvorratsbehälters (2) angeordnet ist.

2. Vorrichtung nach Anspruch 1, in welcher der Arzneimittelvorratsbehälter (3) und der Hautnadelträger (5) aus einem oder mehreren Polymeren aus der Gruppe Polyacrylamid, Carboxymethylcellulose, Polyvinylimin, Polyacrylat, Alginat, Karayagummi und Gelatine aufgebaut sind.
- 5 3. Vorrichtung nach Anspruch 1, in welcher an dem Hautnadelträger (5) 1 bis 15 Stück Hautnadeln (4) je Flächeneinheit (cm) befestigt sind und die Hautnadel (4) den Durchmesser im Bereich von 50 bis 400 µm hat und ihre Länge, die zu der Außenseite des Arzneimittelträgers vorragt, 0,2 bis 2 mm beträgt.
- 10 4. Vorrichtung für transdermale Verabreichung vom Trennungstyp, die als Lappentyp durch Befestigung auf der Haut verwendet wird, mit einer zu der Außenseite hin offenen Elektrode (11) und einem Arzneimittelvorratsbehälter (13), gekennzeichnet durch
  - 15 A) einen Lösungsmittelvorratsbehälter (12) für ionisierendes Lösungsmittel, auf dessen Oberseite die Elektrode (11) ausgebildet ist,
  - B) eine semipermeable Membran (18) mit einem Molekülausschlußbereich von 200 bis 20 000, die die Unterseite des Lösungsmittelvorratsbehälters (12) bildet,
  - 20 C) einen von Arzneimittel überfluteten Arzneimittelvorratsbehälter (13) aus hydrophilem Polymer,
  - D) einen Lappenkörper (30) der aus einer Klebstoffschicht aufgebaut ist, welche um den Arzneimittelvorratsbehälter (13) herum ausgebildet ist, und
  - E) seitlich des Lappenkörpers (30) eine Nadelplatte (15) in welcher mehrere Hautnadeln (14) in einem fixierten Zustand vertikal verteilt sind.
- 25 5. Vorrichtung nach Anspruch 4, in welcher die semipermeable Membran (18) aus der Gruppe Polypropylen, Cellulose und Ethylenvinylacetat ausgewählt ist.

30 **Revendications**

1. Dispositif d'administration transdermique de type intégration sous forme de patch utilisé par fixation sur la peau, comprenant une électrode (1) qui est ouverte vers l'extérieur et un réservoir de médicament (3), caractérisé par
  - 35 A) un réservoir de solvant (2) pour solvant ionisant sur la face supérieure duquel se forme l'électrode (1),
  - B) un réservoir de médicament (3) en polymère hydrophile immergé dans le médicament, formant la partie inférieure du réservoir de solvant (2),
  - C) un support d'aiguilles cutanées (5) en polymère gonflable à l'eau comprenant une multitude d'aiguilles cutanées (4) réparties verticalement à l'état fixe,
  - 40 D) une couche adhésive de structure superposable (6) formée autour dudit support d'aiguilles cutanées (5), et
  - E) une entrée de solvant (7) placée dans la partie centrale supérieure du réservoir de solvant (2).
2. Dispositif selon la revendication 1, dans lequel le réservoir de médicament (3) et le support d'aiguilles cutanées (5) sont composés d'un ou de plusieurs polymères parmi: le polyacrylamide, la carboxyméthylcellulose, la polyvinylimine, le polyacrylate, l'alginat, la gomme de sterculia et la gélatine.
- 45 3. Dispositif selon la revendication 1, dans lequel dans le support d'aiguilles cutanées (5), 1 à 15 aiguilles cutanées (4) sont fixées par unité de surface (cm), et l'aiguille cutanée (4) possède un diamètre allant de 50 à 400 µm, sa longueur saillant vers l'extérieur du support de médicament étant de 0,2 à 2 mm.
- 50 4. Dispositif d'administration transdermique de type séparation sous forme de patch utilisé par fixation sur la peau, comprenant une électrode (11) qui est ouverte vers l'extérieur et un réservoir de médicament (13), caractérisé par
  - 55 A) un réservoir de solvant (12) pour solvant ionisant sur la face supérieure duquel se forme l'électrode (11),
  - B) une membrane semi-perméable (18) ayant un seuil de coupure moléculaire qui varie entre 200 et 20 000 tout en formant la face inférieure dudit réservoir de solvant (12),
  - C) un réservoir de médicament (13) en polymère hydrophile immergé dans le médicament,
  - D) un corps de patch (30) composé de couche adhésive formée autour dudit réservoir de médicament (13), et

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E) en dehors du corps de patch (30), une plaque d'aiguilles (15) dans laquelle une multitude d'aiguilles cutanées (14) sont réparties verticalement à l'état fixe.

5. Dispositif selon la revendication 4, dans lequel la membrane semi-perméable (18) est dans le groupe constitué par le polypropylène, la cellulose et le vinylacétate d'éthylène.

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FIG. 1

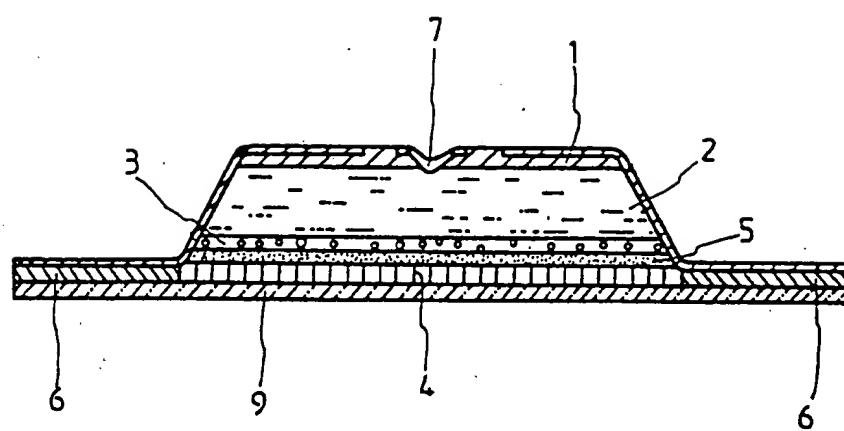


FIG. 2

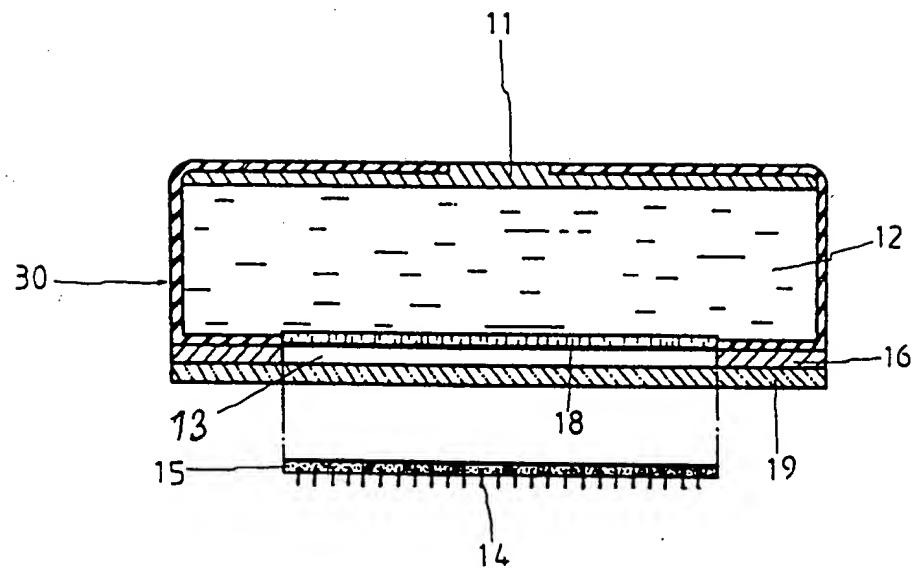
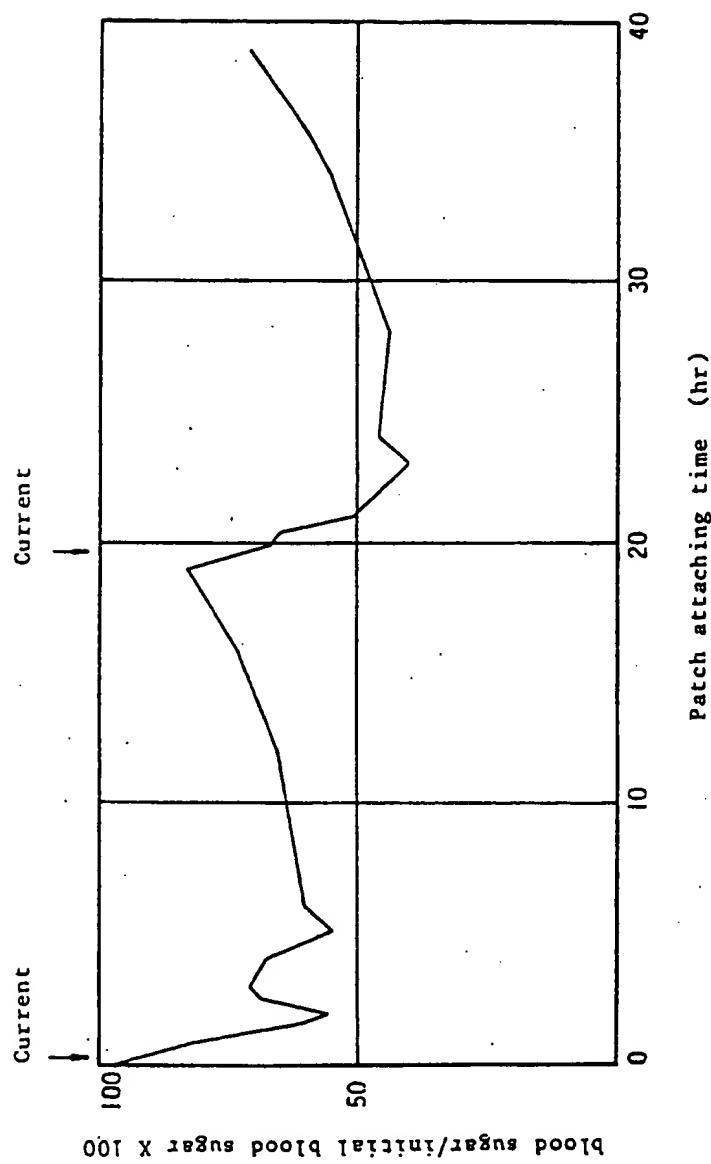


FIG. 3



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